ARTICLE IV.

ON THE RENAL CIRCULATION DURING FEVER. An Experimental Research made at the Pathological Institute of the University of Leipzig. To which was awarded the Cartwright Prize Essay for 1883.[1]

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THE object of this research was to determine by experimental methods the actual condition of the circulation in the kidney during fever.

Heretofore no such experiments have, to our knowledge, been made. Renal pathology has had to content itself with hypotheses founded on the general condition of the circulation as it could be observed in more accessible parts of the body, and on the changes occurring in the urine.

It is perhaps natural that from these insufficient methods wrong conclusions have been drawn. Our work, founded on direct experimentation, has shown the opinion, heretofore prevalent, that the kidney during fever is in a state of congestion, to be wrong. Instead of being swollen, from its vessels being distended with blood, it is, on the contrary, small and shrunken, and in a state of extreme anæmia.

We present in this paper the details of the experiments by which we arrived at the above results, as well as further conclusions derived therefrom.

The work was done during the months of May, June, and July, 1882, in the Physiological Institute of the University of Leipzig, where we have acted under the advice and kind auspices of Professor Cohnheim, who suggested to us the subject and gave us his counsel as to its details. We take the opportunity presented to us here, to express to him our thanks and appreciation for all the facilities so freely offered in carrying on this research.

We employed for our investigations the instrument invented by Roy and used by him in studying the functions of the spleen,[2] and by him and Cohnheim together in studying the kidney.[3] This instrument, called the Oncometer or "bulk-measurer" (for description see pages 386, 387, and 388, Figs. 1 and 2), can be applied to the kidney without, as has been shown by its inventor, interfering with the functions of the organ, and it affords at all times an exact index to the condition of its circulation.

Having had thus placed at our disposal a means by which the *circulation* could be satisfactorily studied, it next remained to hit upon a method of producing the *fever* in the dogs to be used, while they were in that state of complete immobility during the time the oncometer was in use, which is absolutely necessary for success.

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[1] The Cartwright Prize of $500, open to universal competition, is given every other year for the best original research presented to a committee appointed by the Alumni Association of the College of Physicians and Surgeons of New York.

[2] C. S. Roy, The Physiology and Pathology of the Spleen. Journ. of Physiol., vol. iii.

[3] Same. On the Mechanism of the Renal Secretion. Proc. of the Cambridge Philos. Soc., May 23, 1881. Cohnheim and Roy, Untersuchungen über die Circulation in den Nieren. Virchow's Archiv, Bd. lxci. p. 424 (1883).

As a full comprehension of all the methods used is desirable, in order to fairly judge the results obtained, they will be detailed at length.

Methods of producing Fever.—The ordinary means of artificially producing fever in animals has been to inject into a vein or under the skin, pus, or infusions of various organic matters, as hay,[1] for instance. Lately, von Bergmann and Angerer[2] have found that the injection of solutions of pepsin, and of fresh gastric juice into the blood causes a marked rise of temperature, and although we cannot, from want of sufficient proof being adduced, agree with the explanation given by the authors, still the fact we have a number of times confirmed.

The fever produced by these various means has always been in animals not under the influence of drugs which paralyze the motor or sensory functions. We found that when these functions were profoundly affected the expected febrile rise of temperature did not ensue, as was illustrated by the following experiments:—[3]

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[1] Billroth, Langenbeck's Archiv, vol. ii. vi. xiii. C. J. Weber, Berlin. klin. Wochens. 1864.

[2] E. v. Bergmann and J. Angerer. Das Verhältniss der Fermentintoxicationen zur Septicæmie. Festschrift zur Feier des 300-jährigen Bestehens der Universität zu Wurzburg, 1882. These authors hold that the injected pepsin, gastric juice, etc., have the power of dissolving the white blood globules, which leads to a coagulation of the blood, and that all the symptoms, as vomiting, diarrhœa, dyspnœa, etc., are due to capillary thrombosis of the organs in which these symptoms originate. It is not quite clear to us whether they regard the fever as due to a prevention of radiation from the skin on account of the cutaneous capillaries being occluded, but it would almost seem to follow from their statements. Of the actual occurrence of this general capillary thrombosis there are no conclusive proofs, and to our mind it seems much more likely that the symptoms are of nervous origin; the digestive ferments injected into the blood producing a disturbance of the central nervous system.

[3] Since writing the above, N. Zuntz has published a short article entitled "Zur Theorie des Fiebers" in the *Centralblatt f. d. med. Wissenschaften*, No. 32, August 12, 1882, in which he describes obtaining results in curarized dogs, identical to ours. Zuntz concludes, rather hastily it seems to us, that the febrile process in general is due to increased oxidation caused by the irritation of the nerves by pyrogenous agents, and as the muscles are the chief seat of tissue metamorphosis, consequently—he argues—when the terminal nerve-plates are paralyzed by curara, the oxidizing powers of the muscular tissue become paralyzed also, and no fever ensues.

This assumption, however, does not tally with our cases where there was absence of fever in animals under the influence of *morphine*, where the nervous supply of the muscles was in nowise affected. Much more investigation, and especially calorimetrical determinations like those of Senator, Wood, etc., are necessary before such a complex question, involving so many different factors, can be definitely decided.

Our own opinion is that the absence of fever is due to some central nervous cause, but whether inhibitory or irritative in nature we would not venture to say.

Experiment No. 2.—Injection of pus after morphine. May 12th, 1882. Dog. Weight 6500 grams. 10.40 A. M. Temp. 39.3° C. in rectum.

Time.	Temp.	Remarks.
10.40 A. M.	39.3° C.	Injected 0.06 morphine hypod.
10.45	......	Vomited and defecated. Beginning to grow quiet.
10.50	......	Losing power in legs; sinks to floor.
11	38.4	Injected beneath skin of left thigh 25 c.c. fresh pus, free of all odour, and containing very few bacteria.
11.15	37.5	Asleep, but easily awakened by any sudden noise. Covered up.
11.55	36.4	Lying on side; quiet, but not asleep.
12.30 P. M.	36.3	
2	36.4	
2.45	36.8	Running about in an uneasy, aimless sort of way.
3.45	37.2	
7.45	39.4	
May 13th.		
9.30 A. M.	40.8	Listless and dejected. No appetite.
11.15	40.6	

In this experiment but 0.06 of morphine were injected; an amount barely sufficient to put the dog asleep for any length of time, let alone to produce a deep narcosis, yet the temperature sank from 39.3° to 36.3° in a little less than two hours, in spite of the fact that a quantity of pus had in the mean time been injected,—pus which in another dog, not morphinized, caused a rise of temperature from 36.3° to 39.9° in forty-five minutes. Nor till nearly nine hours after the purulent injection, and when the effects of the morphine may be fairly assumed to have passed away, had the temperature risen to its original value. The next morning the dog was dejected, ate nothing, and in fact presented all the outward symptoms of having fever. The temperature was 40.5°, and remained at about that height during the day, showing that the lack of fever in the beginning was not due to the pus having lost its fever-producing properties, but to the action of the morphine upon the system.

Experiment No. 12.—In a healthy dog weighing 5420 grams, and having a temperature of 39.2° C. at 10.30 A. M., 20 c. c. of hay infusion were injected into a vein. The infusion was two days old, had no putrid odour, but contained a large number of bacilli. At 1 P.M. the temperature had risen to 40.6° C. when 14 c. c. of the same infusion were injected hypodermatically, and the animal placed in a warm-air chamber, having a temperature of about 20° C. This last precaution was taken to prevent excessive radiation, the day being somewhat cool. In the meanwhile the dog had become much dejected, vomited frequently, or made attempts to do so, and had had several movements from the bowels. At 2.5 P. M., three hours and thirty-five minutes after the first injection, the temperature was 41.5° C., a rise of 2.3° C., proving conclusively the power of this infusion to cause fever. The dog afterward recovered fully.

Experiment No. 13.—Injection of hay-infusion after (morphine and) curara. June 15th, 1882. Bitch. Weight 4970 grams.

Time.	Temp.	Remarks.
9.50 A. M.	39.4° C.	Before any operative interference.
10	......	Injected hypod. 0.02 morph, and after exposing left kidney for the oncometer, and performing other necessary operations, injected into vein 3 c. c. of a ½ per cent. sol. of curara (which had to be followed at intervals by more).

Time.	Temp.	Remarks.
11.30 A. M.	......	Put in warm box (temp. about 30° C.), and injected into vein 25 c. c of same hay-infusion that was used in the experiment just detailed.
11.40	34.4° C.	
12.10 P. M.	34.2	
12.30	34.2	
12.55	34.4	
1.25	34.6	
1.45	34.7	

A small quantity of morphine was given in the beginning to sufficiently dull the pain of the operation, and the curara administered immediately before the oncometer was applied to the kidney. During the hour and a half used in performing the necessary operations (which aside from the larger one of exposing the kidney, included the minor ones of laying bare the carotid and inserting a canula for connection with the manometer, besides preparing a vein for the injection of curara and hay-infusion), the temperature fell five degrees, part of which was due to the depressing effects of the morphine and curara, and part to the operation itself. However, in spite of putting the animal in the most favourable condition to prevent loss of heat by radiation, the temperature, after injecting the hay infusion, rose but three-tenths of a degree in two hours.

Experiment No. 19.—Injection of pepsin. June 24th, 1882. Dog. Weight 6000 grams (same dog that was used in Exp. 12, now perfectly recovered).

Time.	Temp.	Remarks.
10.55 A. M.	39.7° C.	
11	......	Injected into vein 5 grms. pepsin in 50 c. c. water. (Pepsin did not dissolve completely.)
11.45	40.9	Trembling violently (chill); much dejected.
12.20 P. M.	40.8	
1	41.4	
1.30	42.2	Condition unchanged, but trembling ceased.
6	39	Evidently feels better. Vomited a good deal during afternoon.

This rapid rise of temperature coincides with the results obtained by von Bergmann and Angerer.

Experiment No. 22.—Injection of pepsin after chloral. June 28th, 1882. Dog. Weight 4000 grams.

Time.	Temp.	Remarks.
10.45 A. M.	......[1]	Injected about 5 grams of chloral in solution into stomach.
11.15	36.6° C.	Dog very drowsy, but not completely narcotized. Injected about 3 grms. pepsin in 50 c. c. water (filtered solution) into vein, and put dog in a warm box at a temperature of 25°.
11.30	35.5	
12	35.2	
2 P. M.	......	Dog so far recovered as to be able to walk about.
4.30	40.2	Tremors; much dejection.
6.15	39.9	
June 29th.		
10 A. M.	39.9	Dog eats little, and is dejected. (Subsequently recovered entirely, and was used for another experiment.)

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[1] By an oversight the temperature of the dog before giving the chloral was not taken.

This experiment, like those performed with morphine and curara, shows that after giving the chloral, a primary fall of temperature took place, which lasted as long as the effects of the drug were present. Not till the power of the chloral had sensibly diminished did the pyrogenous agent begin to assert its presence in the organism, by causing a rise of temperature.

The results of the experiments made to produce fever in narcotized animals (and more than are here enumerated were performed, and all with a like result) may therefore be summed up as follows :—

In dogs in which complete motor or sensory paralysis (or both) have been produced by morphine, chloral, or curara, there is a rapid and considerable fall of the bodily temperature, even when radiation is to a great degree prevented by inclosing the animals in a warm-air box. Injections into the blood of pyrogenous agents, such as pus, hay-infusion, and pepsin, fail to cause a rise of temperature as long as the system is under the effects of the drugs used.

Morphine, chloral, and curara were the only agents employed, but it is likely that other similar drugs would act in the same way.

Having thus been defeated in our attempts to cause fever in dogs by all the ordinary means, under the conditions necessary for the experiment, a number of trials were made with the oncometer in curarized dogs in which an artificial rise of temperature was produced by keeping them inclosed in a warm-air chamber. In this way, it is almost needless to say, very high temperatures (up to 45.5° C.), could without difficulty be maintained. The results of these experiments will be given further on.

The warm-air chamber consisted simply of a galvanized sheet-iron box with double sides and bottom, the space between being filled with water kept hot by Bunsen burners placed beneath. In the walls of the box were suitable openings for the insertion of thermometers. For a cover, a double layer of thick felting was found to be the most convenient.

However interesting and instructive the results were obtained with the artificial *thermic* fever (if we adopt the nomenclature of H. C. Wood[1]), still it might well be objected that as thermic fever is not yet universally acknowledged to be identical in its nature with infectious and other fevers, so the deductions drawn from experiments on the former would not hold good when applied to the latter. Some other method, therefore, had to be contrived in which the source of the fever should be internal and not external, and in which the dog should still be insensitive enough to allow of a successful application of the oncometer.

Wood,[2] in his experiments on fever, found that lesions of the brain above the vaso-motor centre in the medulla, produced no change in the arterial blood pressure. The thalami optici are supposed to contain the sensory tracts; consequently, we thought, destruction of these centres might render the animal operated on insensible to pain, while its power of reacting to pyrogenous agents would remain unimpaired.

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[1] H. C. Wood: Thermic Fever or Sunstroke, Philada. 1872.

[2] Same. Fever, a Study in Morbid and Normal Physiology. Smithsonian Contributions to Knowledge, No. 357, Washington, 1880.

On consulting Professor C. Ludwig on the feasibility of this plan, he informed us that he had for some time used this method himself for producing immobility in animals in which he was studying the functions of the various cardiac nerves, and had found that no change, either in the blood-pressure or the heart's action, occurred after this lesion of the brain. His mode of operating consists in trephining the skull about five mm. on either side of the median line, so as to avoid the longitudinal sinus, and at the point of the greatest cranial convexity, which lies four to five centimeters in front of the prominent occipital tubercle. After making a small slit in the dura mater a blunt glass rod of about two mm. in diameter is gently pushed down, directly vertically, toward the base of the skull, till it strikes the bone. The operation, as far as the brain is concerned, is almost bloodless, and it will be found that in nearly every case the thalamus has been punctured.

Dogs so operated on are, for all the purposes of the experiment, immobile and insensitive enough to allow of the perfect application of the oncometer, and furthermore, it was found that injections of pyrogenous agents caused the desired rise of temperature. As hitherto our promptest results had been obtained from injections of pepsin; this agent was used in these experiments.

The following experiment is detailed here; for others, see Experiments Nos. 24 (p. 403) and 25 (p. 393).

Experiment No. 23.—Injection of pepsin after puncture of right thalamus. June 28th, 1882. Bitch. Weight 3300 grams.

Time.	Temp.	Remarks.
12.30 P. M.	39.8° C.	Before any operation.
1.10	......	Punctured right thalamus.[1] Dog's body turned to left, and has "circus movements" in same direction. Anæsthesia apparently on both sides, and blindness. Sensorium much affected.
1.45	39	Injected a filtered solution of 2 grms. pepsin in 40 c. c. of a 0.6 per cent. solution of NaCl.
2	38.8	Put in warm-air box, temperature about 25°.
3.15	39.7	Lying quietly.
4.30	40.4	
5.45	40.3	
6.10	40.3	Removed from box. Condition much the same as in the beginning. Drinks water when offered it, and notices when called. Head wound dressed with iodoform.

June 29th. 10.30 A. M. T. 39.8° C. Circus movements not so marked, though body, when dog stands quietly, is turned to left. Soon sinks on right side when left alone. Licks itself, and notices when called. Growls and tries to bite when handled. No appetite.

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[1] It was found that the puncture of one thalamus was sufficient for practical purposes, and that the temperature rose more rapidly and higher than when both thalami were destroyed.

July 3d. Dog eats well. Circus movements gone. Some anæsthesia on both sides, more on right. Wound in scalp healing well.

Unfortunately, no *post-mortem* examination of the brain was subsequently possible, as the dog escaped from the yard in which it was confined, and was seen no more. It may, however, be safely assumed that the thalamus was punctured in this instance, for in the eight other times, in which this operation was performed, *post-mortem* examination showed that the thalamus had always been reached.

Having thus determined upon a method of producing fever in dogs which would satisfy the conditions of the research, it next remained to investigate, by means of the oncometer, the effects of this fever on the circulation of the kidneys.

Description of Apparatus.[1]—The oncometer of Roy[2] is an ingenious application to organs *in situ* of the plethysmograph of Mosso.[3] The principle of its action, like that of the latter instrument, depends on the expansion of the organ under investigation (due to an increased amount of blood entering it), displacing a quantity of some surrounding liquid, as oil, equal in amount to the increase in volume the organ has undergone. By means of suitable mechanical appliances these variations in bulk, transmitted to the surrounding liquid, are registered graphically upon the revolving drum of Ludwig's kymograph.

The Oncometer.—The oncometer, as constructed for the kidney, consists of an ovoid box of sheet-copper, and is composed of two symmetrical halves joined by a hinge, A (Fig. 2). Each half is made up of two shells, B B′, the inner fitting accurately into the outer. By means of the nut, C, which plays upon the tubular screw, D, soldered into an opening at the point of greatest convexity of the inner shell, and projecting through a corresponding opening in the outer shell, the two may be drawn closely into apposition with each other. Into the tubular screw, D, fits the double canula, E, composed of a larger and a smaller tube, as shown in the figure.

At the large canula, F, connection is made with the writing-apparatus, to be described later, whilst the smaller, G, serves to allow any air-bubbles to escape that may have remained after the instrument has been filled with oil. At a point on each half of the box opposite to the hinge there is a semicircular piece cut out of each edge, which makes a round opening, H, when the box is closed. This opening is provided with a brass collar, K, holding the eccentric catch, L, which keeps the instrument shut when in use. Through this opening the vessels, nerves, and ureter of the kidney pass, as is shown diagrammatically in Fig. 2 (where M represents the kidney, and N the vessels, nerves, and ureter), the thick, rounded edge of the brass collar, K, preventing their being sharply bent or injured in any way.

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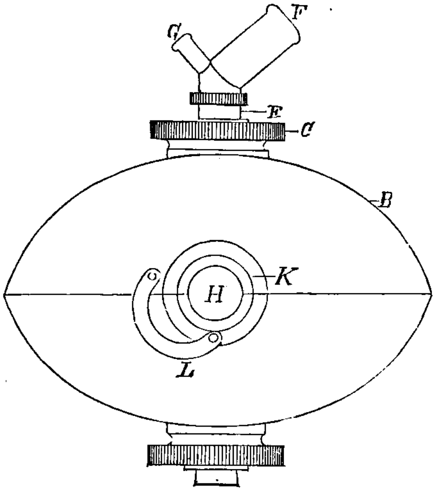
[1] This apparatus may be procured of Mr. Max Schanze, Machinist to the Pathological Institute of Leipzig.

[2] C. S. Roy, The Physiology and Pathology of the Spleen, Jour. of Physiology, vol. iii. No. 3.

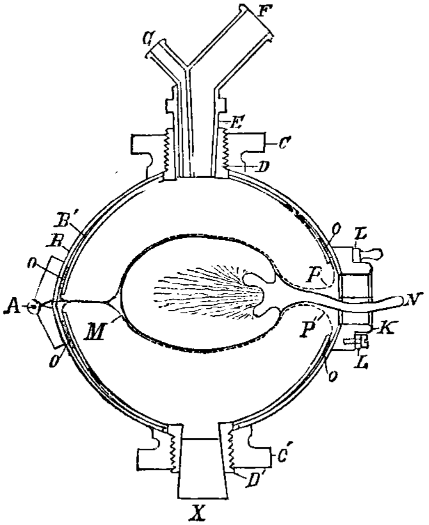
[3] A. Mosso, Von einigen neuen Eigenschaften der Gefässwand, Ludwig's Arbeiten, 1874.

Fig. 1.



When the oncometer is to be used, both the inner shells are removed by unscrewing the nuts, C C′. Around the rim of each, half a centimeter

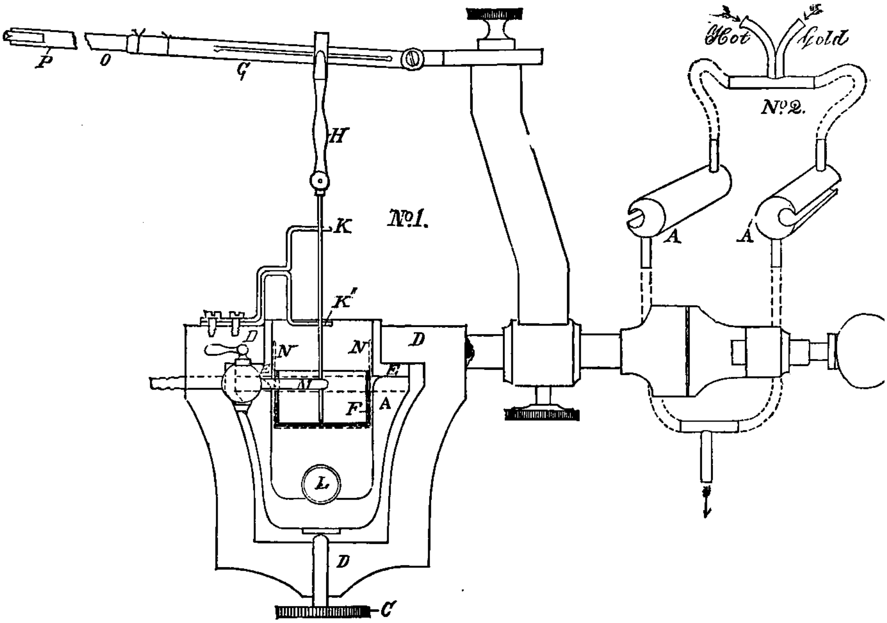
Fig. 2.



from the edge, a flat rubber band (shown in section at O O, Fig. 2), upon which caoutchouc varnish is smeared, is stretched to serve as a washer.

Over the concavity of each of the inner shells a piece of moistened calf's peritoneum[1] is loosely laid, the edges turned over, and pressed against the varnish on the washers, and the inner shells are then replaced and brought firmly against the outer ones by the nuts C C′. Each half of the oncometer consists now of a separate chamber, bounded on the outside by the copper shells, and on the inside by the membrane, P P′ (dotted line). These chambers are next filled full with olive oil, to the exclusion of all air. A quantity of oil, a little less in amount than it is calculated the kidney will occupy, is then pressed out by raising the membranes with the fingers from beneath, whilst the box is so held that the opening for the canulas is highest. This manœuvre is repeated for each half in turn. One opening is closed with a well-fitting cork, X, whilst into the other, the double canula, having rubber tubes on each of its arms, is inserted. The canula and tubes are then emptied of the air they contain by pressing the oil up into them, and are kept closed by spring clamps placed upon the tubes.

Fig. 3.



The Oncograph.—The writing apparatus for recording graphically the changes in the bulk of the kidney (or other organs) has been called by Roy the oncograph. (Fig. 3.)

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[1] After numerous experiments with other membranes, Roy found this one to answer all conditions, it being thin, flexible, impervious to, and unaffected by oil. See Journal of Physiology, vol. i. p. 454; vol. ii. p. 325; vol. iii. p. 205, etc.

Briefly, it consists of a cylinder, A, which by means of the screw, C, may be firmly held against the flat, annular flange, E, of the frame, D. Within the cylinder is an exceedingly thin and light piston-head, F, made of hard rubber, which is connected above with the lever, G, by the jointed piston-rod, H, passing through the guides, K K′. The lower joint of the piston-rod consists of a delicate steel wire, whilst the upper and the lever, G, are of aluminium, in order that their weight shall offer the least resistance to slight impulses received by the piston-head. Between the cylinder, A, which receives the oil, and the flange, E, is clamped a piece of the same membrane used before (shown by the dotted line, N), which prevents the escape of the oil from between the cylinder and the piston. Through the brass tube, L, the oil within the cylinder is connected with that in the oncometer by means of short glass tubes, connected by bits of rubber tubing.

When the cylinder is to be filled, the piston is pressed down as far as the membrane will allow it to go, the cock of the tube, M, is opened, and oil is then allowed to enter from a height through the tube L, the air escaping through M. When the cylinder is entirely full, a clamp is put upon the rubber tube connected with L, and the piston pressed downwards until the lever stands at any desired angle, the surplus oil escaping through M, the cock of which is then shut. The lever is lengthened by tying to it a culm of straw pressed flat, and which has a small piece of aluminium, P, bent and pointed to act as a style, attached to its end by sealing-wax.

Preparation of the Animal.—The dog (animals weighing from five to seven kilos were commonly used), after having been rendered insensible or immovable by one of the means already described, was placed upon its right side, and, after shaving the skin of the left flank,[1] an incision extending from the lower border of the last rib nearly to the crest of the ilium was made. The muscles and fasciæ were then cut through, layer by layer—any large vessels that bled being ligated, and the larger nerves being cut—until the line of aponeurotic junction between the sacro-lumbalis and the oblique and transverse abdominal muscles was reached. This was then so incised as to cut the peritoneum as little as possible, and the kidney, enveloped in its fat, drawn carefully out through the wound, and its capsule dissected away. All the small vessels that enter the cortex from the capsule were either tied with fine thread close to the organ, or closed by tortion. The large renal vessels and ureter at the hilus were only so far separated from the loose fat and connective tissue that envelop them as was necessary to allow their free passage into the oncometer. Especial care was taken not to wound the fine plexuses of nerves and lymphatics that surround the renal bloodvessels on all sides.

The kidney having been prepared, the dog was removed to the warm-air box and the oncometer, previously warmed by being placed in hot water, applied. Great care was taken not to allow any air to enter the oil chambers, as the presence of even a small quantity, by its rapid expansion with the rise of temperature in the dog, may cause considerable errors in the interpretation of the traces. To avoid therefore the entrance of air, the following method was, after trial of others, found satisfactory.

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[1] As the left kidney lies somewhat lower than the right, it is more accessible.

The oncometer was filled pretty full of oil in the beginning, as described on page 388, and closed over the kidney. The two halves being then gently pressed together, and the larger tube of the canula being open, the superfluous oil flowed out. As soon as enough had escaped to allow the edges of the two halves to come together, the catch was snapped and a clamp applied to the tube, which was then connected with the writing apparatus, whose tube and the tube of the canula were filled to the top with oil from a pipette before being joined. In this way a continuous connection between the body of oil in the oncometer and that in the oncograph was effected. By raising or lowering the dog the two instruments were next brought on the same level, in order that the column of oil should exert no pressure, either positive or negative, upon the kidney.

As tracings of the general arterial pressure were always taken along with those of the kidney, the left carotid was connected with the registering manometer, the style of the latter being so arranged as to be as nearly perpendicular as possible beneath that of the oncograph.

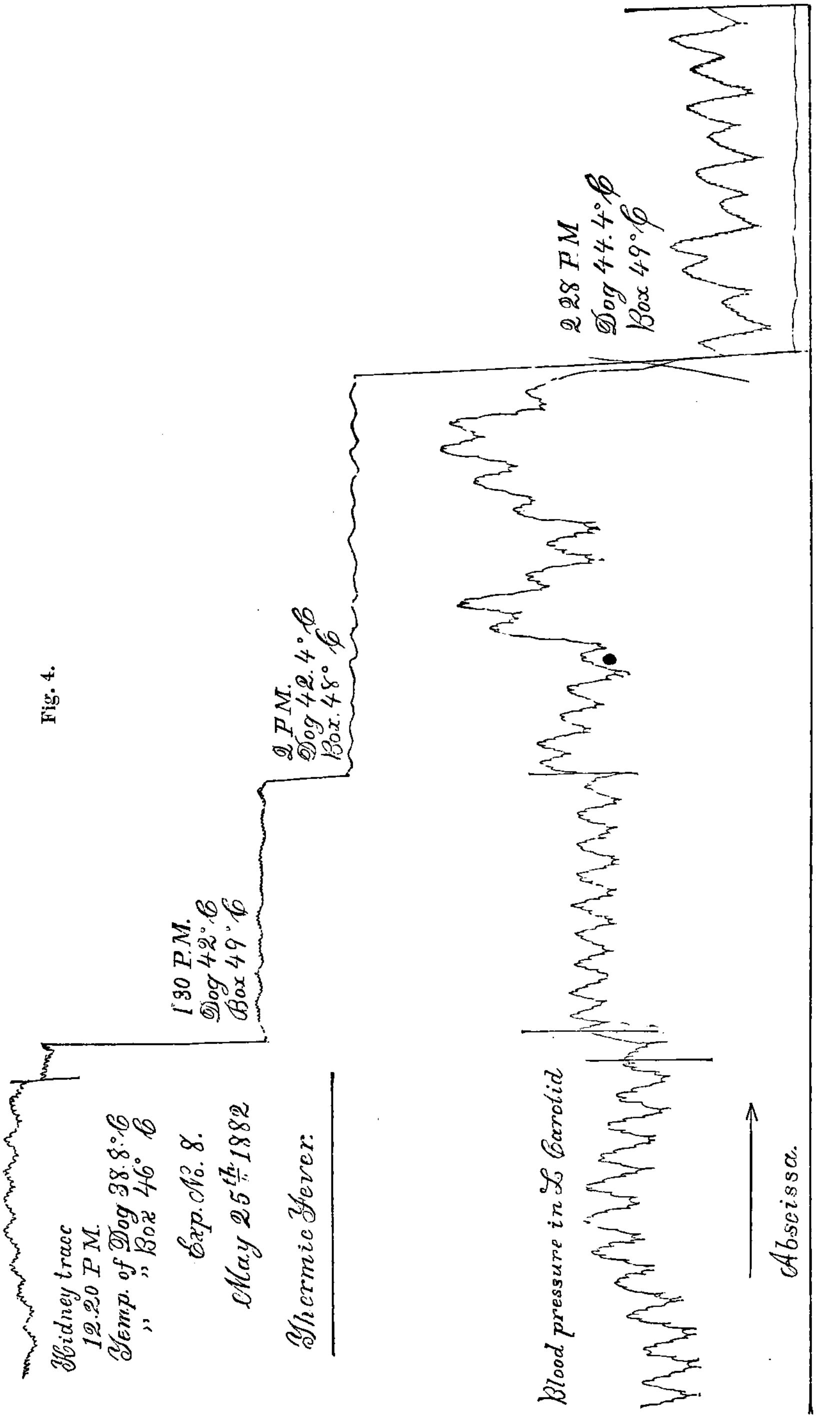
Of the two curves thus traced upon the blackened paper of the kymograph, the upper corresponded to the variations occurring in the bulk of the kidney, and the lower to those in the arterial pressure as measured in the carotid.

On inspecting Fig. 4, it will be seen that the kidney trace consists of a series of waves, each wave being made up of a number of wavelets. The former correspond to the respiratory waves of the pulse, while the latter are the pulse-waves themselves. The accuracy with which these are traced forms a good index to the sensitiveness of the apparatus.

As each experiment always extended over a number of hours, it was, of course, out of the question, and, indeed, unnecessary to take a continuous tracing of the whole duration, but instead, short tracings were made, generally at intervals of from five to fifteen minutes. The temperature of the dog, taken in the rectum or vagina, was noted on the blackened paper at the beginning of each of the sections of which the whole tracing was finally composed. In this way a very graphic impression of the results of the experiment was obtained on a space of paper readily overlooked at once.

It will be observed, on examining Fig. 4, of Experiment No. 8, detailed below, that the kidney tracing constantly approaches nearer and nearer to the abscissa, whilst the mean arterial pressure gradually rises, only to

Fig. 4.


Kidney trace
12.20 P.M.
Temp. of Dog 38.8° C
" " Box 46° C
Exp. No. 8.
May 25th 1882
Thermic Fever.
1.30 P.M.
Dog 42° C
Box 49° C
2 P.M.
Dog 42.4° C
Box 48° C
2.28 P.M.
Dog 44.4° C
Box 49° C
Blood pressure in L Carotid
Abscissa.

fall again when the temperature reaches a point at which life becomes impossible.[1] With each rise in the bodily temperature, there is a corresponding fall in the kidney trace, until at last the pulsations of the kidney become so small that the oncograph fails to register them, and the trace, instead of being made up of a number of curves, now changes to a straight line. The pulse waves disappear first, being the smallest, and these are followed by the respiratory.

The calculation of the amount of diminution in volume which the kidney undergoes was made as follows :—

At the beginning of the experiment (or at its close, it makes no difference which), the oncograph was disconnected from the oncometer, and its tube connected with a graduated burette filled with some of the same oil used for the other apparatus. Oil from the burette was then allowed to slowly flow into the oncograph, one cubic centimetre at a time. As the oil entered, the lever G (Fig. 3) of course rose, its style, P, making an upright trace upon the blackened paper. After the injection of each cubic centimeter the drum of the kymograph was allowed to revolve for a couple of seconds, which caused a horizontal mark, about a couple of millimeters long, to be made at right angles to the former trace.

Thus, a scale was made, the number of whose divisions corresponded to the number of cubic centimeters of oil that had entered the writing apparatus. Each division of this scale was then measured, and was found in this case to be 13 mm.[2] The difference between the height of the lever, as measured from the abscissa, at the beginning and at the end of the experiment, expressed in cubic centimeters of oil, would therefore give the loss in bulk maintained by the kidney during the course of the experiment. The diminution of the kidney's bulk, however, is due to the diminished amount of blood that enters it; therefore, instead of reckoning cubic centimeters of *oil*, the weight of cubic centimeters of *blood* must be taken.

The specific gravity of dog's blood, as we determined it, was 1.061; consequently, it was only necessary to substitute this figure for each cubic centimeter of oil to obtain the loss in weight which the kidney had sustained.

The application of the oncometer, merely to determine the facts regarding changes occurring in the renal circulation during fever, was made in all ten times (seven with thermic, and three times with pepsin fever), and every time, without a single exception, it was shown that *during fever a progressive diminution in the volume of the kidney occurs.*

Two experiments are given here as examples of this :—

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[1] This rise and subsequent fall of the arterial pressure correspond to the results obtained by Senator. See Die Albuminurie im gesunden und kranken Zustande, p. 45. Berlin, 1882.

[2] The length of the divisions of the scale will, of course, vary with the length of the lever.

Experiment No. 8 (Fig. 4).—Thermic fever. May 25th, 1882. Dog. Weight 5 kilos.

Time.	Temp. of dog.	Temp. of box.	Remarks.
10.30 A. M.	39.4° C.	......	Before any operation. Then exposed left kidney, left carotid, and a vein. Curara, and artificial respiration 26 to the minute.
11.35	38.2	......	Put in box.
11.55	38.2	45° C.[1]	
12 M.	38.3	46	
12.20 P. M.	38.8	46	
12.30	39.2	46	
12.55	40.2	47	
1.5	40 6	47	
1.20	41 4	49	Restless; received more curara.
1.30	42	49	Still somewhat restless.
1.40	42.2	48	
1.45	42.4	48	After about every 6th respiration there is a temporary increase of the blood pressure, with a corresponding temporary decrease in the volume of the kidney.
2	43	49	
2.20	44.2	48	
2.35	44.6	51	
2.45	45	52	
2.55	45.4	48	
3.10	......	...	Dog dead. Renal vessels tied, and the organ removed and weighed; weight 24.55 grms.

Calculation.—Height of lever at beginning of experiment, mm. 126
" " " " close " " mm. 2.5

Difference, mm. 123.5

13 mm. on the scale = 1 c.c. oil = 1.061 grm. blood; therefore
123.5 mm. " " " = 9.5 c.c. oil = 10.079 grm. blood; = what the kidney lost in weight during the experiment.
24.55 + 10.079 = 34.629 grm. = original weight of kidney.
Loss of weight = 29.08 per cent.

Experiment No. 25 (Fig. 5).—Pepsin fever after destruction of left thalamus. July 3d, 1882. Dog. Weight 6400 grams.

Time	Temp. of dog.	Temp. of box.	Remarks.
9 A. M.	39.7° C.	......	Before any operation. Punctured left thalamus, then exposed the kidney, and performed the other necessary operations.
11.45	38.6	......	Placed in box, merely to prevent excessive radiation.
11.55	......	......	Injected into vein about 6 grms. pepsin in 100 c.c. water (filtered solution).
12.10 P. M.	38	35° C.	Considerable salivation.
12.20	38.2	35	
1.30	38.9	35	
1.55	39.3	...	
2.30	39.8	35	
3	40.2	30	
3.40	40.5	30	

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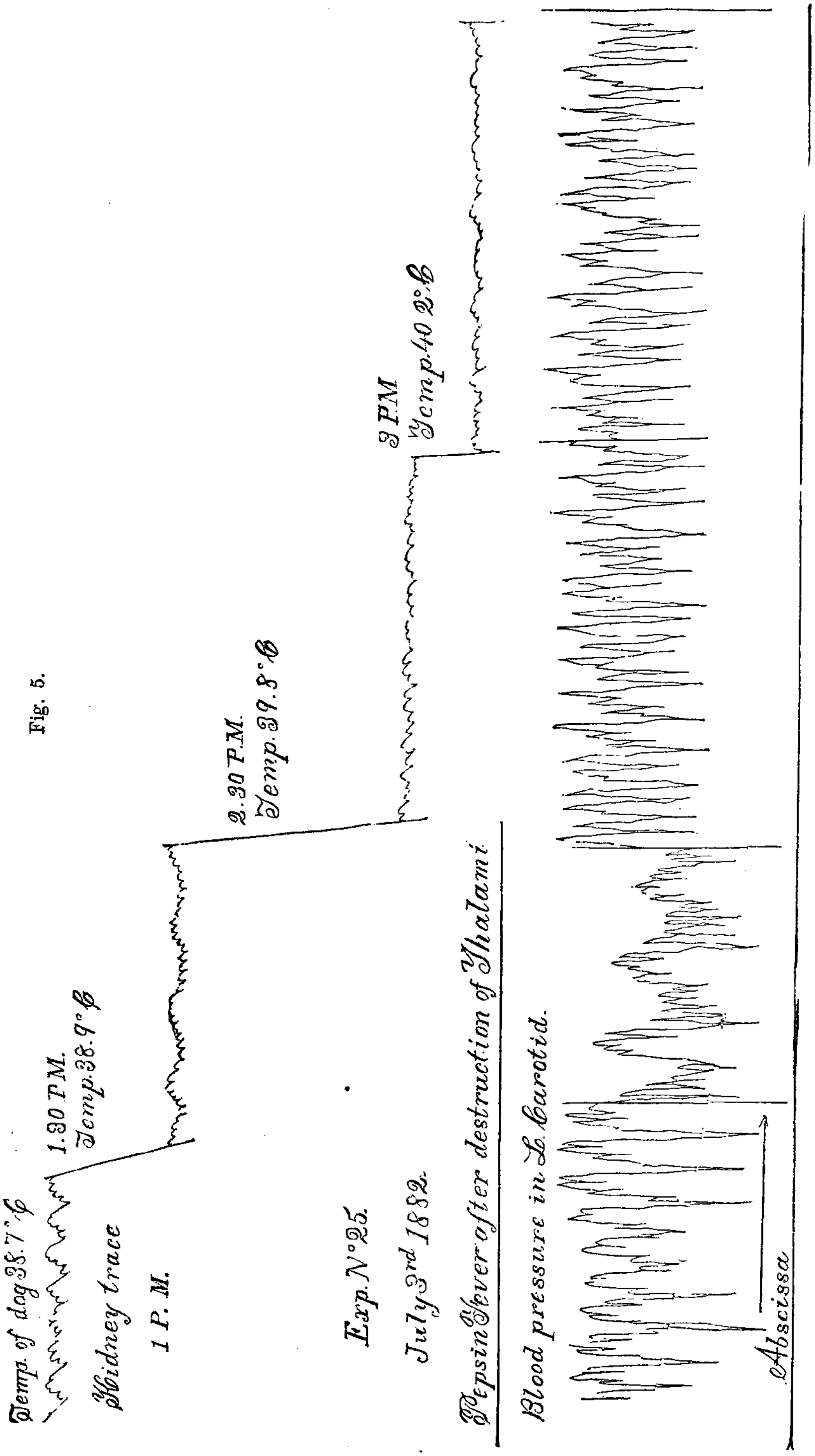
[1] The temperature of the box in all these experiments cannot be taken as the absolute one to which the animals were exposed, as in many cases the cover was left off entirely, or very frequently removed for purposes of examination, and consequently free radiation must have occurred.

Fig. 5.


Temp. of dog 38.7°C
Kidney trace
1 P.M.
1.30 P.M.
Temp. 38.9°C
2.30 P.M.
Temp. 39.8°C
3 P.M.
Temp. 40.2°C
Exp. No 25.
July 3rd 1882.
Pepsin Fever after destruction of Thalami
Blood pressure in L. Carotid.
Abscissa

Time.	Temp. of dog.	Temp. of box.	Remarks.
4.50 P. M.	41.2° C.	28° C.	Dog restless; mouth dry; drinks water when given it. Respiration at times very jerky. Has spasms of extensor muscles of limbs and trunk.
5.40	41.9	28	
6.10	41.8	28	
6.15	41.6	...	
6.20	......	...	Tied renal vessels, and removed kidney. Weight 21.2 grms. Dog killed.

Post-mortem Examination.—Left thalamus extensively destroyed. The lower half of the right thalamus has been punctured in a direction from the median line.

Calculation.—Height of lever at beginning of exp't (temp. 38 6°), mm. 155
“ “ “ “ close “ “ (temp. 41.9), mm. 105

Difference, mm. 50

13 mm. on the scale = 1 c.c. of oil = 1.061 grms. of blood; therefore
50 mm. “ “ “ = 3.85 c.c. of oil = 4.08 grms. of blood = what the kidney lost in weight during the experiment.
4.08 + 21.2 = 25.28 grms. = original weight of kidney.
Loss of weight = 16.14 per cent.

The following are the estimations of the loss of weight the kidney sustained in different experiments.

	No.	Thermic fever.	Pepsin fever.
Experiment No.	7,	31.14 per cent.	....
“ “	9,	20.33 “	....
“ “	10,	32.49 “	....
“ “	11,	23.12 “	....
“ “	24,	....	7.88 per cent.
“ “	25,	....	16.14 “

As it could be supposed that this contraction of the renal vessels, causing the loss in bulk of the kidney, might take place in non-fevering dogs as well, merely from the irritation due to the presence of the oncometer, several experiments were made to settle this point. The oncometer was applied to the kidney and left on for several hours, the bodily temperature being normal. It was found, however, that the kidney retained its original volume throughout, but began to contract as soon as fever was afterward superinduced.

Determination of Cause.—The fact of the kidney's diminished volume having been thus definitely determined, it now remained to investigate the causes.

That changes in the volume of the kidney must depend on the amount of blood contained in its bloodvessels at any one time, becomes evident when we consider that the kidney is an organ which, outside of these vessels, contains no contractile elements.

Variations in the volume of blood caused by changes in the calibre of the renal capillaries may take place either from a central irritation, a peripheral irritation, or a combination of the two.

Peripheral Irritation.—Roy and Cohnheim have shown that when the nerves of the kidney are intact a contraction of the organ, consentaneous with the rise of the general arterial pressure, occurs when a peripheral stimulus is applied to any part of the body. This reaction may be used as a test to determine whether the connections between the nervous centres and the kidney have been completely severed or not.

Section of the nerve trunks supplying the kidney is always a tedious operation, and at best an uncertain one, as the origin and course of the nerves are subject to considerable variation.[1] We found it better, instead of severing the main branches, to carefully tear away with a pair of delicate forceps, all the nerves that could be seen entering at the hilus, and as these surround the vessels in a close plexus, considerable care is requisite to clean them away thoroughly. The ureter was divided about an inch from the hilus, in order to cut off all nerves entering on it.

It was found in the majority of cases, that after this operation had been carefully done, the kidney no longer, or but slightly reacted to peripheral stimulation, showing conclusively that all, or by far the greater number of renal nerves must have been divided. As intra-renal ganglia have not to our knowledge been discovered, it was *a priori* to be supposed that after severance of the nervous connections no change would occur in the kidney during a rise of temperature. This supposition proved to be correct.

Experiment No. 33.—Kidney enervated. Thermic fever. July 20th, 1882. Dog. Weight 5400 grams.

Time.	Temp. of dog.	Temp. of box.	Remarks.
10.30 A. M.	39.5° C.	......	Before operation. Gave morphine 0.04 hypo. and later curara. Artificial respiration. Kidney exposed and enervated of all visible nerves, and ureter cut.
12	36.9	......	Faradic stimulation of sciatic causes rise in arterial pressure, but kidney remains almost unaffected.
12.45 P. M.	38	45	
1	38.9	52	
1.15	39.7	42	
1.55	40.7	42	
2.5	41.6	...	Dog killed.

On inspecting Fig. 6, corresponding to this experiment, it will be seen that after a faradic stimulation of the sciatic the arterial pressure became increased, while the kidney underwent but a very slight enlargement. At first sight it might be supposed that the kidney trace ought to follow in parallel lines that of the arterial pressure, rising and falling with it, but that it does not do so, but remains, on the whole, nearly parallel to the abscissa, may be explained by the fact that when the renal nerves are severed, the capillaries, owing to lack of tonus, at once dilate nearly to their maximum capacity, and being thenceforth always in a state of engorgement, cannot be filled much fuller, even when a general rise of arte-

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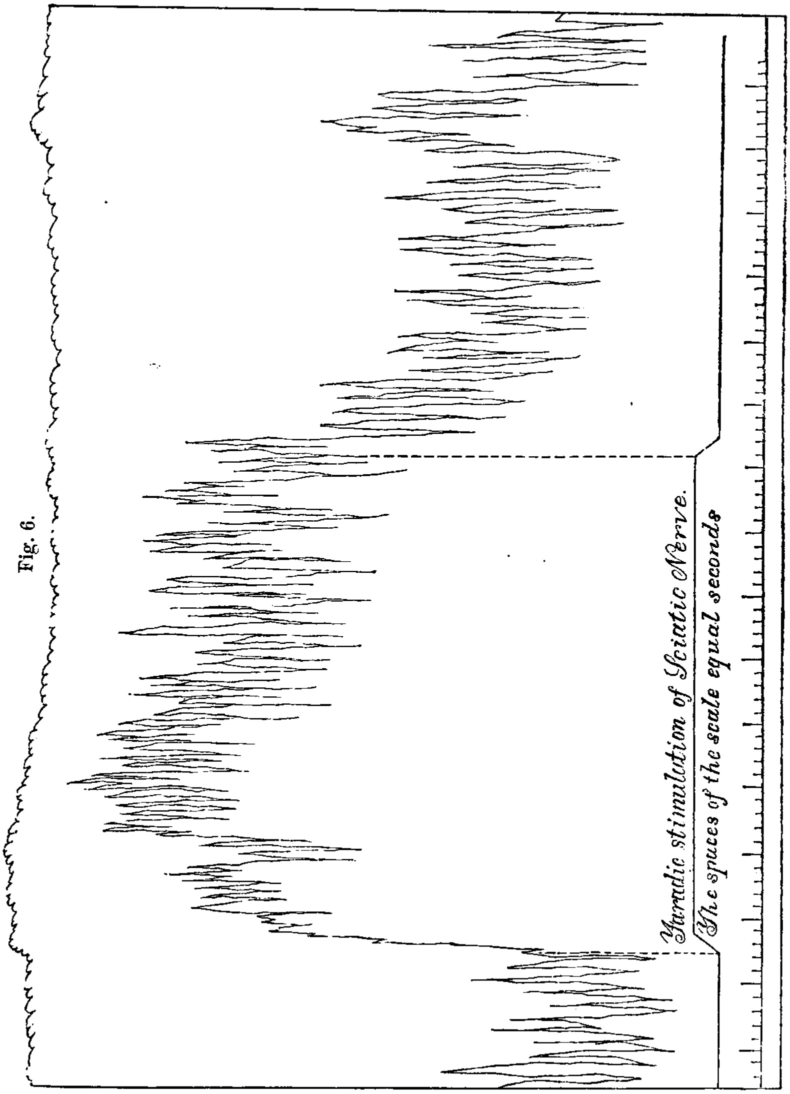
[1] Fr. Nöllner, Die Anatomie des Splanchnicus und der Nierennerven beim Hunde. Eckhard's Beiträge zur Anatomie und Physiologie. Giessen, 1869.

Fig. 6.



rial pressure occurs. That the arterial tonus is much diminished, if not gone entirely, is confirmed by the separate pulse-waves of enervated kidneys being usually larger than of those in which the nerves have been left intact.

It was several times observed that strong faradic stimulations, applied to the sciatic immediately after the enervation, failed to produce any contraction of the kidney, whereas, after an hour or two, when these stimulations were reapplied, a slight reaction of the organ was registered by the tracing; but the degree of this reaction was always very small compared to that of uninjured kidneys. This phenomenon may be explained by assuming that after the operation those nerves that had escaped being cut must, at all events, have been considerably bruised, and thus for a time rendered unfit for conducting purposes. After a period of rest, however, they recovered their function, allowing the reflex effects of a peripheral stimulus to reach the kidney, and to cause there a contraction of those few vessels, the conduction of whose nervous supply had not been permanently destroyed. So fine and almost invisible are the nerves that enter the kidney on the sheaths of the vessels that whilst it is possible to sever by far the greater number of them, some few are almost sure to escape in every case. Practically, however, the presence of these remaining fibres does not interfere with the interpretation of the result of the experiment, for the difference between the tracing of the non-enervated kidney of a fevering dog and the enervated organ is too striking not to be at once apparent.

Whilst the former, as we have seen, approaches constantly the abscissa as the temperature rises, *the mean curve of the latter pursues an almost parallel course.*

Spinal Cord.—Still another method of severing the connection between kidney and brain remained, and that was to perform section of the cord, but, as was expected in the beginning, the results obtained in this manner were not so satisfactory as those afforded by the direct enervation. The possible connections between brain and kidney by way of the sympathetic are so numerous and complicated[1] that, no matter at what level the cord is cut, one can never be sure of being above the point of exit of all the supplying nerve branches. Section of the cord, even when performed low down, has also the disadvantage that the arterial pressure subsequently sinks to a very low point, and that a rapid fall of temperature occurs. In consequence the dogs stand the operation badly; death occurring two or three hours after.

In every case where section of the cord was made, however, results tallying closely with those cases of enervation where it could be fairly assumed that a certain number of nerves had escaped, were obtained. It was found that the kidney tracing remained almost uninfluenced by the rise of bodily temperature, and that, although the kidney could be made to slightly contract by applying a very powerful faradic stimulus directly to a bared nerve, as the median or sciatic, yet this reaction was almost nil when compared to that which takes place when the cord is intact.

Local Fever.—Further determinations regarding the central or peripheral origin of the renal contraction were made by causing a local fever, as

[1] Nöllner, op. cit.

it were, in the brain, whilst the kidney and the rest of the body remained of normal temperature. This was done by means of the apparatus invented by Goldstein for studying the dyspnœa of fever.[1]

This apparatus (see Fig. 3, No. 2) consists of a brass water-jacket fitting pretty closely around the carotid, and through which hot or cold water can be made to flow from vessels connected with it by rubber tubes. In order to insure a more prompt heating of the brain each carotid was provided with such a jacket, and the water was made to pass through both simultaneously. Between the hot jackets and the surrounding tissues several layers of thick, dry filter paper were laid which were found sufficient to prevent the vagus and other nerves being irritated by the heat.

Hot water of a measured temperature was allowed to run through for a certain length of time, a mark being made on the trace at the beginning and at the end. After the hot, some cold water was run through the brass jackets to cool them.

It was noted in all the experiments that in a few seconds after the hot water had entered the jackets the tracing registered a contraction of the kidney, while the general arterial pressure gradually rose. There was a latent period of varying length before the contractions began, and they lasted a short time after the hot water had been shut off and cold had been turned on, the kidney resuming then quite, or very nearly, its original volume and the blood pressure falling to its former height.

This reaction to a direct *central* irritation appeared so constantly and with such promptness that no misinterpretation of its significance was very well possible.

It may be remarked, by way of parenthesis, that we were fully able to corroborate Goldstein's observations regarding the dyspnœa that occurs during the temporary heating of the brain by hot blood, inasmuch as the appearance of rapid respiratory movements, becoming in some cases almost convulsive in nature, were regularly noticed every time the blood in the carotids was heated.

It might perhaps be urged that the change in the kidney was due reflexly to the sensation of asphyxia present, as shown by the dyspnœa, and of which the violent attempts at respiration were the exponent. That this however was not the cause, was proved by the arterial pressure remaining unchanged. Ordinarily, when asphyxia is produced, the general arterial pressure begins to rise a few seconds before the kidney begins to contract.

Taking the results of all the experiments made into consideration, we think it justifiable to draw the following conclusion :—

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[1] Ueber Wärmedyspnoë, L. Goldstein. Arbeiten aus dem physiologischen Laboratorium der Würzburger Hochschule. A. Fick, 1872.

The decrease in the bulk of the kidney during fever is due to a contraction of its vessels which, in all probability, is the result of a stimulus conveyed to them from the central nervous system; the stimulus being the consequence of irritation of the central vaso-motor centres by the abnormally hot blood circulating through them during fever.

We have purposely said "in all probability," for Mosso,[1] in his investigations into the properties of the walls of the bloodvessels, has found that a contraction or dilatation of the vessels of extirpated kidneys takes place according as certain drugs, such as atropine, nicotine, etc. etc., are added to the blood with which these kidneys are fed. Still, however instructive these results may be from a purely physiological point of view regarding the vessels only, and not the kidney as a whole, they should hardly be considered as having too much weight when applied to the results of this research, because the kidney as it exists and functionates in the body of a living animal is, after all, a thing very different from one extirpated, even though the latter be kept, so to speak, *alive* for days, as in Mosso's experiment, by maintaining an artificial circulation through it. From this reason we refrained from repeating Mosso's experiments, and using hot blood, considering that no matter what the results might be they would be of little value in this case, in either proving or disproving the *central* origin of the vascular contraction.

General Conclusions.—From the experiments made we have proved:—

1. That in dogs with fever the kidney undergoes a diminution in its bulk.
2. That this diminution is due to a contraction of the walls of the bloodvessels; and,
3. That it is constant and progressive, being proportionate to the intensity of the fever.
4. That it is in all probability the result of a nervous stimulus, originating in the central (cerebral) nervous system from the irritation of abnormally hot blood circulating there.

From the intimate relations existing between the arterial pressure and the secretion of the urine, it will at once be evident that many of the changes occurring in the latter during fever may be readily explained by considering the above-named facts. Thus the *decrease in the amount of urine* secreted by fever patients, which has heretofore been ascribed to the increased loss of water through the lungs and skin (and which may amount to one-half,[2] or even a third,[3] of that normally secreted), becomes all the more explicable when the marked contraction is considered, which we have here shown that the renal vessels undergo during fever. For in this case it is immaterial whether we accept the theory of Ludwig and his pupils, that the amount of urine secreted is dependent on the height of the arterial pressure in the kidney, or that of Heidenhain, that it is due to the rapidity of the blood-current in the renal vessels. In either case the great contraction of the kidneys' vessels would produce both a diminished blood-pressure and a retarded current within the organ, and hence a lessened secretion of urine.

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[1] A. Mosso. Von einigen neuen Eigenschaften der Gefässwand, Ludwig's Arbeiten, 1874.

[2] Cohnheim, Allgemeine Pathologie, vol. ii. p. 568, 2d ed. Berlin, 1882.

[3] Senator, Untersuchungen ü. d. fieberhaften Process. etc., p. 123. Berlin, 1873.

The occurrence of *albuminuria*, such a constant symptom in nearly all high fevers, becomes readily understood when we bear in mind the extreme anæmia which we have seen affects the kidney during a hyperpyrexia. For nearly all authorities are now agreed that albuminuria is due to the glomerulal epithelium, in consequence of being insufficiently nourished with arterial blood, losing its function of retaining within the vessels the albuminous portions of the blood plasma.[1] The extreme sensitiveness of the renal epithelium generally to anæmia, whether partial or complete, has been shown by many observers,[2] and it is not surprising therefore, that in consequence of the prolonged and marked anæmia in the kidneys of fevering individuals, the epithelium should be so profoundly affected as to seriously impair its function, and allow it to become permeable to albumen.

It must be remembered that the foregoing experiments relate to fevers which, however high, were but of some hours' duration, and which would therefore come under the head of acute. It may not be out of place, however, to call attention to the fact that even in those cases of excessively high temperature, one example of which is recorded in Experiment No. 8, p. 393, where toward the close, when death was imminent, and it is probable that a general relaxation of all the vital functions was occurring, as is shown by the irregular and feeble action of the heart, and the presence of the marked Traube-Hering curves (Fig. 4, toward the end, at T. 42.4°), still, even in these instances, we say, the kidney remains in a state of complete contraction to the last. We point to this as having some analogy, perhaps, to cases of chronic fever, where what the temperature fails to attain by intensity, it makes up by quantity and duration; and that even in chronic fever the condition of the kidney, as regards its circulation, may possibly not be different to that in acute attacks. This is but a surmise which would need the test of further experiment to prove or refute.

Many other interesting questions to be solved in this connection present themselves. Thus, the actual measurement of the urine during an experimental fever to determine the mutual relations between the amounts secreted, the temperature, and the degree of contraction of the kidney.

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[1] R. Heidenhain, Hermann's Handbuch der Physiologie, vol. v. p. 371, 1881. Cohnheim, Allgemeine Pathologie, 2d ed., vol. ii. p. 321, 1882.

[2] Max Hermann, Sitzgsber. d. Wiener Acad. Math. phys., Cl. lxv., 1861. R. Overbeck, same, lxvii., 1863. M. Litten, Untersuchungen über den hæmorrhagischen Infarct. Berlin, 1879; and others.

Then the relation between the renal circulation and the cutaneous. All these and many more require to be investigated before our knowledge of the renal circulation during fever will be in any sense complete. Incomplete in many ways as the author feels this research to be, he offers it as the first contribution toward the founding of an understanding of the renal pathology of fever based on experimental investigation, hoping it may be but the beginning of a series which will clear up this most important subject. For at present we have been groping in the dark, forced to content ourselves with theories based on analogies, and having actually no *positive* data based on experiment on which to found our views.

APPENDIX.—Although not strictly belonging here, we think it well to record the following observations noted in the course of the experiments :—

In a number of cases it was found that the arterial pressure rose with the increasing bodily temperature of the dog, a diminution occurring when the temperature had risen to a point incompatible with life, and when a general state of collapse had begun.[1] If, after the arterial pressure had risen in consequence of fever, the dog was cooled off, not only did the blood-pressure sink again, but the kidney increased in volume.

The following are some tables giving the amount of arterial pressure at different temperatures.

Experiment No. 8.—Thermic fever. May 25th, 1882.

Time.	Temp. of dog.	Arterial pressure.	Temp. of box.
12.20	38.8° C.	104 mm. of Hg.	46° C.
12.30	39.2	104 " "	46
12.55	40.2	112 " "	47
1.5	40.6	114 " "	47
1.15	41.4	116 " "	47
1.30	42	116 " "	49
1.45	42.4	130 " "	49
2	42.4	136 " "	48
2.7	43.3	140 " "	50
2.15	44	120 " "	49
2.20	44.2	112 " "	48
2.28	44.4	80 " "	50
3.10	Dog died.		

On inspecting Fig. 4, of Experiment No. 8, it will be seen that the Traube-Hering waves become very marked, and the individual heart-beats very small and frequent as the temperature approaches lethal limits, though the mean arterial pressure does not begin to fall until some time after both these phenomena have put in their appearance. It is highest at 42.4° C. (136 mm. of mercury), and then rapidly falls, being twenty minutes after, at the time of death, but 80 mm., the temperature being then 44.4°.

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[1] Senator, Die Albuminurie im gesunden und kranken Zustande, p. 45. Berlin, 1882. See, also, Paschutin, Ludwig's Arbeiten, 1873, p. 229, and Zadek, Zeitschrift für klinische Medicin, vol. ii. p. 509.

Experiment No. 9.—Thermic fever. June 8th, 1882.

Time.	Temp. of dog.	Arterial pressure.	Temp. of box.	
1	37.8° C.	112 mm. of Hg.	...	
1.40	38.5	100 “ “	48° C.	
2	39.5	110 “ “	52	
2.16	40.2	120 “ “	52	
2.25	40.8	130 “ “	52	
2.40	41.8	144 “ “	52	
2.50	42	172 “ “	52	
3.10	41.1	134 “ “	30	Box cooled off.
3.15	41	140 “ “	25	
3.25	40.6	148 “ “	24	
3.30	Dog died from hemorrhage from the carotid.			

In Experiment No. 9 a continuous rise of arterial pressure, going hand in hand with the increased bodily temperature, took place until the former registered 172 mm. at 42° C. The box being then cooled by allowing cold water to flow through it, the temperature of the dog fell, and with it the blood pressure; the kidney increasing in volume at the same time.

Experiment No. 24.—Pepsin fever. June 30th, 1882.

Time.	Temp. of dog.	Arterial pressure.	Respirations.	
11.15	36.9° C.	120 mm. of Hg.	...	
12.30	37.5	134 “ “	...	
1.15	37.9	134 “ “	...	
1.30	38.3	138 “ “	...	
2.20	38.8	138 “ “	...	
2.52	39.2	156 “ “	...	
3.20	39.6	156 “ “	...	
4.15	40	156 “ “	...	
4.30	40.2	158 “ “	...	
5.30	40.5	160 “ “	130	
6.5	40.5	140 “ “	180	
6.30	40.1	160 “ “	34	Irregular.
6.40	40	160 “ “	20	“
6.50	Dog killed.			

In Experiment No. 24 a continuous rise of arterial pressure took place to the end, when the dog was killed, the temperature being 40° C., and the arterial pressure 160 mm.

Experiment No. 25.—Pepsin fever. July 3d, 1882.

Time.	Temp. of dog.	Arterial pressssure.
11.45	88.6° C.	124 mm. of Hg.
12.20	38.2	108 “ “
1	38.7	116 “ “
1.55	39.3	118 “ “
3	40.2	126 “ “
3.40	40.5	120 “ “
4.50	41.2	140 “ “
5.10	41.7	136 “ “
5.55	41.9	120 “ “
6.10	41.8	104 “ “
6.20	Dog killed.	

Here the pressure increased till it was 140 mm. at 41.2° when it began to decline, the temperature still rising. At 41.8° the dog was killed, it having then sunk to 104 mm.